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Review

Mosquito-borne viral diseases and potential transmission blocking vaccine candidates

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ABSTRACT

Mosquito-borne viral diseases (MBVDs) have a complex biological cycle involving vectors and vertebrate hosts. These viruses are responsible for many deadly diseases worldwide. Although MBVDs threaten mostly developing countries, there is growing evidence indicating that they are also of concern in western countries where local transmission of arboviruses such as West Nile, Zika, Chikungunya and Dengue viruses have been recently reported. The rapid rise in human infections caused by these viruses is attributed to rapid climate change and travel facilities. Usually, the only way to control these diseases relies on the control of vectors in the absence of licensed vaccines and specific treatments. However, the overuse of insecticides has led to the emergence of insecticide resistance in vector populations, posing significant challenges for their control. An alternative method for reducing MBVDs can be the use of Transmission Blocking Vaccines (TBVs) that limits viral infection at the mosquito vector stage. Some successes have been obtained confirming the potential application of TBVs against viruses; however, this approach remains at the developmental stage and still needs improvements. The present review aims to give an update on MBVDs and to discuss the application as well as usage of potential TBVs for the control of mosquito-borne viral infections.

1. Introduction

Arboviruses (arthropod-borne viruses) do not represent a unique monophylogenetic group, but share a common mode of transmission through arthropods, especially mosquitoes (Contigiani et al., 2017). Around 50 arboviruses are pathogenic for humans and animals (Contigiani et al., 2017). Approximately 40 mosquito-borne flaviviruses have been identified (Mackenzie et al., 2004). Vector-borne diseases are responsible for 22.8% of emerging infectious diseases that affect human and animal health (Jones et al., 2008). Mosquito-borne viral diseases (MBVDs) continue to contribute significantly to epidemics that disrupt health security around the world. The impact of MBVDs is largely influenced by the worldwide distribution of mosquitoes that act as vectors (Otranto and Dantas-Torres, 2016). Effective strategies are urgently needed to combat such arboviruses which are mainly based on vector control (McGraw and O'Neill, 2013). Most arboviruses transmitted by mosquitoes, act primarily as zoonotic pathogens and their emergence as human pathogens coincides with intensive urbanisation and changes in land use offering the conditions suitable for mosquito proliferation at close vicinity of high human densities (Vasilakis and Gubler, 2016). For a long time, it was thought that arboviruses threaten only developing countries. However, emerging and re-emerging pathogens such as West Nile virus (WNV), Zika virus (ZIKV), Chikungunya virus (CHIKV) and Dengue virus (DENV) are spreading beyond their natural range of distribution, posing threats to temperate regions. Control of MBVDs relies primarily on the use of insecticides. Since 1970s, mosquito control strategies are confronted with the emergence of insecticide-resistant populations within vector species (Liu, 2015; Sparks and Nauen, 2015), stressing the need to develop new approaches.

Among them, paratransgenesis which corresponds to the genetic modification of symbiotic microorganisms, such as bacteria has become a promising tool for vector control (Arora and Douglas, 2017). Some bacteria which have developed a stable association with their mosquito hosts can be genetically manipulated for mosquito control (Wilke and Marrelli, 2015). Another strategy is limiting the replication of viruses with *Wolbachia* endosymbiont. It is theorized that the presence of *Wolbachia* activates the insect immune system which confers the protection against subsequent infection by viruses or creates a competition between *Wolbachia* and viruses for host cellular resources (Terradas et al., 2017). The *Wolbachia* *w*Mel strain is able to block DENV and

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invade *Aedes aegypti* population (Bian et al., 2010; Walker et al., 2011). Therefore, *Wolbachia* can be considered as a powerful tool for prevention of the future MBVD outbreaks like Zika fever (Caragata et al., 2016). Recent investigations suggest that Zika control programs can be facilitated by the use of *Wolbachia pipientis* (McGraw and O'Neill, 2013; Caragata et al., 2016). Transmission of ZIKV can be interrupted by the *w*Mel *Wolbachia* (isolated from *Drosophila melanogaster*), *w*AlbB (isolated from *Ae. albopictus* mosquitoes) and *w*Stri (isolated from *Laodelphax striatellus*) (Schultz et al., 2017). *Aedes aegypti* populations infected with the *w*Mel *Wolbachia* strain have been released successfully in many countries in order to control DENV transmission (Caragata et al., 2016). *Wolbachia* may also inhibit the replication of other arboviruses such as CHIKV, Yellow Fever virus (YFV) and WNV (Yakob and Walker, 2016; Joubert and O'Neill, 2017).

Recently, Transmission Blocking Vaccines (TBVs) have been shown to be a new promising approach. Different from traditional vaccines, altruistic TBVs aim to prevent infection of the vector including mosquitoes when getting a blood meal on the vaccinated vertebrate host, reducing the transmission capacity. TBVs aim at preventing the transmission of pathogens from infected to uninfected vertebrate hosts by targeting molecule(s) expressed on the surface of pathogens during their developmental phases within the insect vector or by targeting molecules expressed by the vectors (Rener et al., 1983). The genesis of TBV concept coincided with the first description of the etiologic agent of malaria (Laveran, 1880) until Huff et al. (1958) who reported that vaccination with whole asexual and sexual parasites induced transmission-blocking immunity. To the best of our knowledge, the majority of TBV candidates come from the studies which using targets of *Plasmodium* parasites (Zakeri et al., 2009; Coutinho-Abreu and Ramalho-Ortigao, 2010; Jones et al., 2015; Chaurio et al., 2016; Mehrizi et al., 2014, 2016) or targets of mosquito tissues (Gholizadeh et al., 2010; Bokharaei et al., 2012; Raz et al., 2013; Atkinson et al., 2015). Antimalarial TBVs have shown promises as effective tools to inhibit the transmission of malaria parasite. The *Plasmodium* life-cycle shows that the transmission reduction would be most effective when the targeting of parasite be done within the mosquito body (Sinden, 2010); here, the ingested antibodies by *Anopheles* mosquito during a bloodmeal prevent the sexual development of *Plasmodium* by binding to the mosquito-derived antigens (Niu et al., 2017) or on the surface proteins of the parasite (malERA Refresh Consultative Panel on Tools for Malaria Elimination, 2017). The phase I clinical trial of *Plasmodium falciparum* P25 (Pfs25), which is the *P. falciparum* derived TBV, have been performed in 2008 (Wu et al., 2008) and field trials are underway (Talaat et al., 2016). However, this approach remains at its developmental stage.

Updated information of most important mosquito-borne viruses is needed for designing effective TBV candidates. Designing vaccines that prevent the completing of arbovirus life cycle in the mosquito is an approach to interrupt its transmission to vertebrate hosts (Londono-Renteria et al., 2016). In order to control MBVDs, TBVs are relying on immunization of vertebrate hosts with mosquito derived molecules for interrupting the pathogen transmission from infected to uninfected hosts. Such molecules may be inoculated into the vertebrate host as formulated purified proteins for inducing the host immune system and producing specific antibodies (Fig. 1).

2. Important mosquito-borne viruses

Among Flaviviruses (Family: Flaviviridae), Japanese encephalitis virus (JEV) is transmitted mainly by *Culex tritaeniorhynchus* and *Cx. vishnui* (Leake et al., 1986; Chu et al., 2017). This virus is distributed mainly in Asia (Mackenzie et al., 2004). St. Louis encephalitis Virus (SLEV) is related to JEV; this virus is transmitted by *Culex* species (Reisen, 2003) and is mainly distributed in North and South America (Kopp et al., 2013). Mosquitoes from the genus *Culex*, become infected by feeding on infected birds.

WNV is transmitted mainly by *Cx. tarsalis, Cx. quinquefasciatus, Cx. stigmatosoma, Cx. thriambus, Cx. pipiens* and *Cx. nigripalpus* (Colpitts et al., 2012); however, the lineages 2 and 5 of WNV have been recently isolated from *Aedeomyia madagascarica*, *An. pauliani* in Madagascar and *Cx. pseudovishnui*, *Mansonia uniformis* in India, respectively (Maquart et al., 2016; Khan et al., 2017). This virus is distributed in Africa, southern Asia, and northern Australia, and sporadically in more temperate regions of Europe (Petersen et al., 2007; ECDC, 2014). In a study carried out in 2015, potential for co-infections with a mosquito-specific flavivirus, Nhumirim virus (NHUV), was investigated to block WNV transmission in mosquitoes (Goenaga et al., 2015). YFV is transmitted mostly by *Ae. aegypti, Ae. furcifer, Ae. taylori, Ae. luteocephalus, Ae. africanus, Ae. simpsoni, Ae. vittatus* and *Ae. Opok*. This virus is maintained through the Amazon basin in a jungle cycle involving non-human primates and mosquitoes of the *Haemagogus* and *Sabethes* genera (Barrett and Higgs, 2007). This virus is today mainly distributed in Africa and Latin America (Vasconcelos, 2010; WHO, 2012; Markoff, 2013). Yellow fever vaccine 17D (YF-17D) is considered as an available effective vaccine. ZIKV is mainly transmitted by *Ae. aegypti* (Boyer et al., 2018). Originated from Africa, this virus is now distributed in South America, Central America, the Caribbean, the Pacific region and Southeast Asia (Fauci and Morens, 2016; WHO, 2016a). Murray Valley encephalitis Virus (MVEV) is transmitted by *Cx. annulirostris* and is distributed in West Australia and Papua New Guinea. The last outbreak of MVEV occurred in 1974, and 58 cases of encephalitis were identified (Bennett, 2008), indicating the significance of this disease despite the infrequency of epidemics.

CHIKV, Eastern equine encephalitis virus (EEEV), Mayaro virus (MAYV), Venezuelan equine encephalitis virus (VEEV) and Western equine encephalitis virus (WEEV) are alphaviruses (Family: Togaviridae). CHIKV was first isolated from serum of a febrile patient in Tanzania in 1953 (Ross, 1956). This virus is transmitted mainly by *Ae. aegypti* and *Ae. albopictus* (Horwood and Buchy, 2015); the virus is now distributed in Africa, Americas, Asia, Europe and Oceania (Busch and Erickson, 2015). MAYV circulates in tropical forests or rural areas of Central and South America causing a disease that, in some patients, can persist for long periods and may be misinterpreted as Chikungunya (Esposito and da Fonseca, 2017). As outbreaks of VEEV occurred in Central and South American countries, Venezuelan equine encephalitis (VEE) becomes the most important arboviral disease affecting the central nervous system (CNS) in the Americas (Seymour and Weaver, 2016). EEEV and WEEV are distributed mainly in the US.

Rift valley fever virus (RVFV, *Phlebovirus*: Bunyaviridae) was isolated for the first time from a lamb in Kenya in 1930 (Daubney et al., 1931). *Aedes* and *Culex* species are considered as the main vectors (Gerdes, 2004) but ticks (Linthicum et al., 1989; Nchu and Rand, 2013) and sand flies (Dohm et al., 2000) are also able to transmit the virus. This virus is mostly distributed in Africa (Gerdes, 2004).

Viruses that are transmitted by mosquitoes are mostly enveloped. Mutations affecting genes of the viral envelope may confer varying degrees of replicative advantage (Tsetsarkin et al., 2011, 2016). Envelope (E) proteins are responsible for not only receptor binding but also for membrane fusion. Mutations that affect either functions can hinder or enable parasite infection (Tsetsarkin et al., 2016); in fact, shifts in vector species of emerging viruses can be caused by an adaptation of viruses to a new vector host with enhanced viral replication and transmission (Hwang et al., 2016). For example, CHIKV is mainly spread by *Ae. aegypti*, but a mutation within the E1 protein responsible for fusion arose in the Indian Ocean lineage that confers a 100-times growth advantage in *Ae. albopictus* (Tsetsarkin et al., 2007; Vazeille et al., 2007); however, no significant effect on transmission was observed in *Ae. aegypti* (Tsetsarkin et al., 2011, 2016). Selection of this new CHIKV epidemic variant is likely to have occurred in the midgut of the mosquito (Arias-Goeta et al., 2013). The mosquito midgut cDNA library can then be a valuable tool to identify proteins that serve to viral replication and interactions with ingested arboviruses. The use of

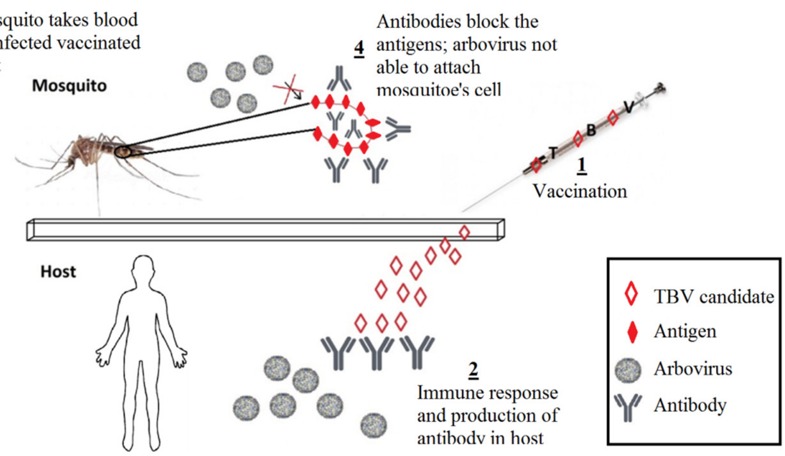

Fig 1. TBVs block the pathogen propagation and prevent transmission of pathogens by the bite of arthropod vectors.

proteomics can also be solicited in order to identify the proteins modulated after viral infection.

3. Potential TBV candidates

Epidemics of MBVDs are easily affected by changes in natural environments, social circumstances and recent increase in traveling facilities. Recent investigations have shown that prevalence of MBVDs is not limited to the tropics anymore. It has been demonstrated that ZIKV, DENV and CHIKV were easily transmitted locally in temperate countries. For these three viruses, both models and human case data have shown that transmission occurs between 18 and 34 °C with maximal transmission occurring in a range of 26–29 °C (Mordecai et al., 2017). Findings suggest that the spread of these diseases in non-tropical areas and temperate regions such as South America and northern Mexico is more likely than expected. To prevent infections with arboviruses, surveillance must be reinforced. Associated with the mapping of larval habitats, evaluation of mosquito adult activity, detection of symptomatic cases should lead to the implementation of more adapted control measures. However, all these methods are time consuming and sometimes less accurate than expected due to local variations in arboviral transmission features (Schmidt, 2016). Here, we suggest the evaluation of TBVs against MBVDs in order to prevent the transmission of arboviruses among the people at risk. The litterature was examined for potential TBV candidates against arboviruses transmitted by mosquitoes (Table 1). Therefore, the following candidates are described.

3.1. Alpha-glucosidase

Alpha-glucosidase is involved in carbohydrate metabolism. It is up-regulated in DENV-2 infection (Tchankouo-Nguetcheu et al., 2010). Due to its important role in arboviral infection in mosquito midgut cells, Alpha-glucosidase inhibitors have been shown to eliminate the replication of arboviruses like DENV-2 (Wu et al., 2002). It has been revealed that alpha-glucosidase has an important role in DENV-2 infection in mosquito midgut; also, this enzyme favors virus survival, replication and transmission, suggesting a subversion of insect cell metabolism by arboviruses (Tchankouo-Nguetcheu et al., 2010).

3.2. Carboxypeptidases

In insects, the activity of Carboxypeptidase A (CPA) or B (CPB) has been found in the midgut of many insect species. Studies on *An. gambiae* and *An. stephensi* revealed that polyclonal antibodies against CPB and CPA can block sexual development of *Plasmodium* in the mosquito midgut (Lavazec et al., 2007; Raz et al., 2013; VenkatRao et al., 2017). Overexpression of CPB1 in mosquito cells results in intracellular DENV-2 genomic RNA or virus particles accumulation, with a lower amount of virus release. Therefore, in *Ae. aegypti* midgut cells, CPB1 binds to the E protein deposited on the endoplasmic reticulum intraluminal membranes and inhibits DENV-2 RNA encapsulation, thus limits budding from the endoplasmic reticulum, and interferes with immature virus transportation to the trans-Golgi network (Tham et al., 2014; Londono-Renteria et al., 2016).

3.3. Cysteine-rich venom protein

Londono-Renteria et al. (2015) have shown that *Ae. aegypti* populations infected with DENV require a putative cysteine rich venom protein (SeqID AAEL000379; CRVP379). They demonstrated that silencing this gene significantly reduced DENV infection in *Aedes aegypti* cells. They also showed that blocking CRVP379 protein with either RNAi or specific antisera inhibited DENV infection in *Aedes aegypti*.

3.4. Hsp60

Following the infection with arboviruses, Tchankouo-Nguetcheu et al. (2010) have brought out some proteins specifically expressed in the midgut of *Ae. aegypti*: some are involved in cell protection and the modulation of Hsp60 and transferrin, favoring virus replication and transmission. This suggests a subversion of the insect cell metabolism by arboviruses. Hsp60 interferes positively with DENV infection and the level of Hsp60 is up-regulated in the midgut of *Ae. aegypti* infected with DENV-2. Also, the transcription of Hsp60 down regulates by Sindbis virus (Tchankouo-Nguetcheu et al., 2010). However, concerning transferrin, there are reports on up-regulation of transferrin in insects or insect cells challenged with bacteria, suggesting an antibacterial role of this protein (Yoshiga et al., 1997; Nichol et al., 2002), while a down-regulation of transferrin as shown in *Ae. aegypti* model with CHIKV and DENV-2, may favour viral multiplication (Tchankouo-Nguetcheu et al., 2010). Further investigations are needed to find out the functional role of Hsp60 and transferrin in the regulation of infection in other mosquito vector - virus models related to MBVDs. Also, studies using RNAi in mosquitoes are suggested to assess the role of these proteins in viral dissemination and replication within mosquitoes.

3.5. Mosquito galactose specific C-type lectins

Several proteins in arthropods and mammals with carbohydrate-binding activity named C-type lectins are employed as attachment factors to facilitate flavivirus invasion (Liu et al., 2014). There is evidence showing that anti mosGCTL-1 (mosquito galactose specific C-type

Table 1
Details of the potential TBV candidates against arboviruses and their functions in mosquitoes.

	Candidate molecule/pathogen family	Candidate	Arthropod host	Effect on disease	Function
1	alpha-glucosidase	alpha-glucosidase	Insects	Inhibits DENV-2 survival, replication and transmission	Alpha-glucosidase inhibitors are able to eliminate the replication of endoplasmic reticulum-budding viruses (Wu et al., 2002). This enzyme has a role in DENV-2 infection in mosquito midgut cells (Tchankouo-Nguetcheu et al., 2010).
2	Carboxypeptidases	CPB-1	*Ae. aegypti*	Reduces DENV infection in mosquitoes	Binds to the E protein deposited on the ER intraluminal membranes and inhibits DENV-2 RNA encapsulation, thus inhibits budding from the ER, and may interfere with immature virus transportation to the trans-Golgi network (Tham et al., 2014; Londono-Renteria et al., 2016).
3	Cysteine rich venom protein	Cysteine rich venom Protein	*Ae. aegypti*	DENV requires this protein for infecting Mosquitoes	Interacts with the putative DENV receptor prohibitin; DENV infection of *Ae. aegypti* requires this protein (Londono-Renteria et al., 2015)
4	Glycoproteins	Glycoproteins	Mosquitoes	Blocks the virus targets	Potential universal disease transmission blocking targets (Dinglasan et al., 2005).
5	Hsp60	Hsp60	*Ae. aegypti*	Hsp60 protein interferes positively with DENV infection. The transcription of Hsp60 down regulates by Sindbis virus	The level of Hsp60 is up-regulated in *Ae. aegypti* infected with DENV-2 (Tchankouo-Nguetcheu et al., 2010).
6	*mosGCTL*	*mosGCTL*-1	*Ae. aegypti*, *Cx. quinquefasciatus*	Reduces WNV infection in mosquitoes	Involved in WNV attachment by interacting with PTP-1 (Cheng et al., 2010); Immunoprecipitation experiments revealed that this protein strongly interacted and bound to WNV virions (Cheng et al., 2010).
		mosGCTL-3	*Ae. aegypti*	Reduces DENV infection in mosquitoes	Modulates virus entry by interacting with the DENV E protein (Liu et al., 2014).
		mosGCTL-7	*Ae. aegypti*	*mosGCTL*-7 mediates JEV infection	*mosGCTL*-7 binds to the N-glycan at N154 on the JEV E protein. This recognition of viral N-glycan by *mosGCTL*-7 is required for JEV infection (Liu et al., 2017).
		mosGCTL-15, 19, 20, 22, 23, 24, 26, 32	*Ae. aegypti*	Reduce DENV infection in mosquitoes	Modulate virus entry by interacting with the DENV E protein (Liu et al., 2014).
7	*mosPTP*	*mosPTP*-1	*Aedes sp.*, *Culex sp.*	*mosPTP*-1 participates in WNV and JEV endocytosis	Secreted *mosGCTL*-1 enhances WNV infection by interacting with the virus and bridging it to the *mosPTP*-1 cellular receptor (Perera-Lecoin et al., 2013). mosPTP-1 facilitates JEV infection in *Ae. aegypti* (Liu et al., 2017).
8	Saliva	saliva proteins	*Ae. aegypti*	Inhibition/enhancement of DENV infection	*Aedes aegypti* SGEs enhance dissemination of DENV (Conway et al., 2014); *Ae. aegypti* D7 Saliva protein inhibits DENV infection (Conway et al., 2016). *Aedes aegypti* LTRIN is receptor for ZIKV (Jin et al., 2018).

lectin-1) (Cheng et al., 2010), anti mosGCTL-7 (Liu et al., 2017) and anti mosGCTL-3, 15, 19, 20, 22, 23, 24, 26, 32 (Liu et al., 2014) antibodies are able to decrease the viral load of WNV, JEV and DENV in mosquitoes respectively.

Silencing the paralogous of 9 *mosGCTLs* decreases DENV load in *Ae. aegypti*, suggesting that the virus employs mosGCTLs to enhance the infection (Liu et al., 2014). Multiple members of mosGCTLs including mosGCTL-3, 15, 19, 20, 22, 23, 24, 26 and mosGCTL-32 were able to bind to DENV-2 E proteins (Liu et al., 2014). When microinjecting dsRNA targeting *mosGCTL*s into *Ae. aegypti* and then, infecting with DENV, nine genes were demonstrated to decrease the viral load (Liu et al., 2014). These 9 *mosGCTL*s were induced in mosquito tissues during DENV-2 infection and these proteins interacted with DENV-2 surface envelope (E) protein. This study shows that DENV may employ multiple mosGCTLs as ligands to promote the infection of vectors with mosGCTL-3 exhibiting the most significant effect (Liu et al., 2014). In another study, 36 midgut proteins were identified to interact with DENV-2 (Tham et al., 2015). In *Ae. albopictus*, C-type lectin-1 (*Aalb_CTL1*) expressed specifically in female mosquito salivary glands is a promising candidate: it exhibits agglutinating activity against animal erythrocytes, Gram-positive bacteria and yeast (Cheng et al., 2014).

mosGCTL-7/mosPTP-1 pathway plays a key role in JEV infection in mosquitoes; *mosGCTL-7* by binding to the N-glycan at N154 on JEV E protein modulates viral infection in mosquitoes (Liu et al., 2017). The recognition of viral N-glycan by *mosGCTL-7* is a prerequisite for JEV infection, and this interaction is Ca2 + −dependent. After mosGCTL-7 binds to the glycan, mosPTP-1 binds to mosGCTL-7 and promotes JEV entry. Viral load can be significantly decreased when silencing *mosPTP-1* and completely abolished when injecting anti-mosGCTL-7 antibodies (Liu et al., 2017). In another study, mosGCTL-1 in *Ae. aegypti* and *Cx. quinquefasciatus*, was able to interact with WNV in a calcium-dependent manner, facilitating the virus entry *in vivo* and *in vitro* (Cheng et al., 2010); however, silencing *mosGCTL-1* did not influence DENV infection in *Ae. aegypti*, suggesting that this gene is specific to WNV infection (Cheng et al., 2010; Liu et al., 2014).

Analysis of *Cx. quinquefasciatus, An. gambiae, Ae. aegypti* and *Ae. albopictus* amino-acid sequences related to C-type lectin (CTL)/C-type lectin-like (CTLD) reveals main differences in peptide sequences (Fig. 2). These differences may affect the capacity of mosquito species to be vectors of arboviruses.

3.6. mosPTP-1

It has been proven that secreted mosGCTL-1 in *Ae. aegypti* and *Cx. quinquefasciatus* enhances WNV infection by interacting with the virus and bridging it to the cellular receptor, mosPTP-1, a protein tyrosine phosphatase expressed at the cell surface (Cheng et al., 2010).

Virus entry is facilitated by the binding of complexes of virus/mosGCTL-1 to cellular mosPTP-1 (Cheng et al., 2010). Participation of mosPTP-1 in virus endocytosis is unclear: it acts as an entry receptor or as an attachment factor (Perera-Lecoin et al., 2013). It has been demonstrated that mosPTP-1 facilitates JEV infection in *Ae. aegypti* and mosGCTL-7–mosPTP-1 interaction is an important infection mechanism for this virus in *Ae. aegypti* (Liu et al., 2017). However, mosPTP-1 is not necessary for DENV infection, suggesting that functional redundancy may exist with uncharacterized paralogs (Liu et al., 2014).

3.7. Saliva proteins

Mosquito saliva contains complex peptide mixtures (Schneider and Higgs, 2008) that facilitate transmission of arboviruses. An approach using salivary proteins of mosquitoes might protect against arboviruses (Manning et al., 2018).

Specific antigens in salivary glands of mosquitoes have been targeted to inhibit the development of malaria parasites. For example, in Korochkina et al. (2006), a mosquito-specific protein family in salivary glands of *An. gambiae* was introduced as a receptor for *P. falciparum*; in Brennan et al. (2000), *An. gambiae* salivary gland proteins were introduced as putative targets for blocking malaria parasites; in Okulate et al. (2007), Saglin protein was characterized and introduced as transmission blocking candidate molecule for malaria. Also, Dragovic et al. (2018) revealed that immunization against AgTRIO contributed protection against *Plasmodium* parasite in mice. It has been proved that in these studies, produced antibodies against specific antigens can proceed from the midgut to salivary glands of mosquitoes and block the pathogen development.

Experimental animal data reveal that immunization with some mosquito salivary proteins can augment virus transmission. Salivary protein D7 immunization leads to increased WNV mortality in mice (Reagan et al., 2012). This protein inhibits DENV infection in *Ae. aegypti* (Conway et al., 2016). LTRIN from *Ae. aegypti* has been identified as a receptor for ZIKV (Jin et al., 2018). Another investigation on mice inoculated with *Aedes* salivary gland extract (SGE), was associated with increased DENV titers in the skin, overall infection and migration of skin immune cells, and endothelial permeability (Schmid et al., 2016). SGE of *Aedes* spp. is able to suppress antimicrobial peptide secretion by human keratinocytes, which in turn leads to enhanced DENV replication in these cells (Surasombatpattana et al., 2014). SGEs from *Ae. aegypti* are able to enhance dissemination of DENV to draining lymph nodes. *Aedes aegypti* salivary protein, CLIPA3 protease, promotes DENV replication *via* cleavage of extracellular matrix proteins, liquefying the dermal layer (Conway et al., 2014). The inhibition of proteolytic activity of saliva, by administering a specific blocking antibody to the host, could modulate viral infectivity, in conjunction with a pathogen-based vaccine (Conway et al., 2014).

3.8. Other candidates

Carbohydrates are essential molecules for plethora of cellular processes such as structural support, signaling and protection (Roseman, 2001). Their critical role in infectious diseases models further underscores their promise as vaccine targets (Dinglasan et al., 2003; Monzavi-Karbassi et al., 2003). Sugar epitopes seem to be potential universal disease transmission blocking targets against several vector-borne pathogens (Dinglasan et al., 2005). Additional investigations are needed to understand the function of these epitopes. The proof of concept has been described as MG96 monoclonal antibody completely blocks *Plasmodium* parasite development by targeting the mosquito midgut microvilli carbohydrate epitope or glycotope (Dinglasan et al., 2003).

Two proteins (molecular mass of 60 and 38 kDa) in *Ae. aegypti* midgut are putative gut receptors for CHIKV (Mourya et al., 1998). Also, plasma membrane-associated proteins in mosquitoes are possible receptors for JEV, WNV and DENV-2 (Chu et al., 2005). Mercado-Curiel et al. (2006) have shown that two proteins of molecular mass of 80 (R80) and 67-kDa (R67) in *Ae. aegypti* midgut and *Ae. albopictus* cells are receptors for all DENV serotypes. Enolase, beta-adrenergic receptor kinase, translation elongation factor EF-1 alpha/Tu and cadherin in *Ae. aegypti* mosquitoes and *Ae. albopictus* cells are binding proteins of DENV (Munoz et al., 2013). Another investigation has revealed the role of ATP synthase Beta subunit in CHIKV entry into mosquito cells (Fongsaran et al., 2014).

4. Conclusion

For the vast majority of MBVDs, there is no vaccine alternative. In the late 1990s, the United States (US) suffered the emergence of WNV as well as Central and South America that later had to face the emergence of Chikungunya and Zika (Fernández-Salas et al., 2015; Petersen et al., 2016). The rapid spread of these MBVDs could result from the high densities of anthropophilic mosquitoes such as *Ae. aegypti* whose control has been abandoned since the 1970s in America (WHO, 2016b). Detection of newly introduced viral infections in mosquitoes such as

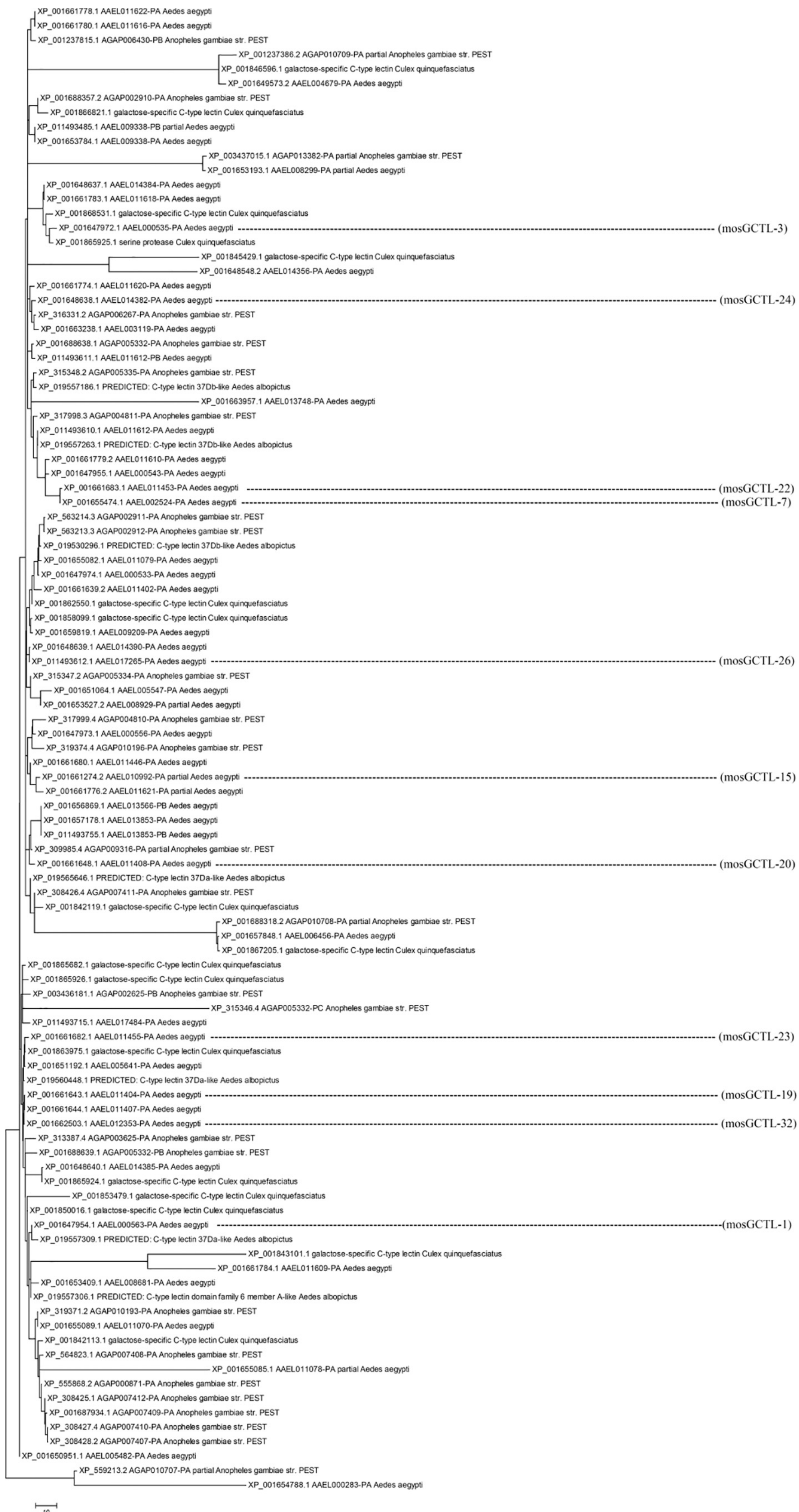

Fig. 2. Molecular phylogenetic analysis of *Cx. quinquefasciatus, An. gambiae*, *Ae. aegypti* and *Ae. albopictus* protein sequences related to C-type lectin (CTL)/C-type lectin-like (CTLD). The evolutionary history was inferred by using the Maximum Likelihood method (Jones et al., 1992). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 103 amino acid sequences. All positions containing gaps and missing data were eliminated. There were a total of 102 positions in the final dataset. Evolutionary analyses were conducted in MEGA7 (Kumar et al., 2016). Important *mosGCTLs* are indicated: anti *mosGCTL*-1 (Cheng et al., 2010), anti *mosGCTL*-7 (Liu et al., 2017) and anti *mosGCTL*-3, 15, 19, 20, 22, 23, 24, 26, 32 (Liu et al., 2014) antibodies are able to block WNV, JEV and DENV respectively.

Parramatta river virus (PaRV), isolated from *Ae. vigilax* in 2015 (McLean et al., 2015) and Palm Creek virus (PCV), isolated from *Coquillettidia xanthogaster* in 2013 (Hobson-Peters et al., 2013), underlines the importance of strenghtening surveillance programs.

As most of the mosquito-borne viruses are enveloped, they are expected to enter target cells by fusion of membranes. These viruses are adapted to both mosquitoes and vertebrates and therefore, exploited evolutionarily conserved pathways shared between the two hosts (Hwang et al., 2016). Arboviruses are able to enter mosquito cells by receptor-mediated endocytosis or by direct fusion of E protein with surface receptors or cell membranes (Franz et al., 2015). The aim of this review was to provide an overview on TBV candidates as a promising tool to control MBVDs. As developing several anti-pathogen TBVs may be impractical, it has been suggested to target molecules which are expressed by the mosquitoes (Dinglasan et al., 2005). Therefore, identification and characterization of the mosquitoes' midgut receptors is suggested for understanding the role of gut receptors in arbovirus entry and consequently, promoting the development of TBV candidates (Neelakanta and Sultana, 2016). The candidate molecules should be critical for the interaction between the vector and the pathogen, compatible with different types of adjuvants, providing functional antibody titer and conserved among pathogen isolates (Neelakanta and Sultana, 2015).

TBVs have now to move to clinical trials (Wu et al., 2008) with particular attention to avoid any cross-reactions or autoimmune disease. Here, we suggest that TBV candidates against mosquito-borne viruses are an important alternative strategy as they are able to block the viruses at the early step of entry in mosquitoes. This strategy has the advantage over the others: to be sustainable, ecologically clean and not disturbing ecological balance between species. It is suggested to do further investigations in order to find a TBV candidate that covers a maximum of arboviruses with a long lasting efficacy and coverage within the populations living or traveling to the arboviral-endemic areas worldwide.

Conflicts of interest

Authors declare no conflict of interest.

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